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     (FILE 'HOME' ENTERED AT 17:09:36 ON 20 MAY 2000)

     FILE 'INPADOC' ENTERED AT 17:13:22 ON 20 MAY 2000
L1             1 S EP 897721/PN

     FILE 'STNGUIDE' ENTERED AT 17:13:57 ON 20 MAY 2000

     FILE 'INPADOC' ENTERED AT 17:14:09 ON 20 MAY 2000

     FILE 'STNGUIDE' ENTERED AT 17:14:38 ON 20 MAY 2000

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:22:03 ON 20 MAY 2000
L2          2483 S (LEUPRORELIN OR CETRORELIX OR BUSERELIN OR ANTIDE OR
RAMORELI
L3           804 S (RALOXIFEN# OR DROLOXIFEN OR CENTCHROMAN)
L4            17 S L2 AND L3
L5            17 DUP REM L4 (0 DUPLICATES REMOVED)
L6             1 S L5 AND GYNECOLOG?
L7             5 S L5 AND PY <=1997
L8            69 S LHRH(3A)(AGONIST# OR ANTAGONIST#) AND (ANTIESTROGEN# OR
ANTI(
L9            34 S L8 AND (GYNECOLOG? OR ENDOMETRIOS? OR MYOMA##)
L10           34 DUP REM L9 (0 DUPLICATES REMOVED)
L11           10 S L10 AND PY<=1996

     FILE 'STNGUIDE' ENTERED AT 17:38:54 ON 20 MAY 2000
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FILE 'CAPLUS' ENTERED AT 17:22:03 ON 20 MAY 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'USPATFULL' ENTERED AT 17:22:03 ON 20 MAY 2000

=> s (leuprorelin or cetrorelix or buserelin or antide or ramorelix or zoladex or lhrh(3a)(agonist# or antagonist#))

L2 2483 (LEUPRORELIN OR CETRORELIX OR BUSERELIN OR ANTIDE OR RAMORELIX OR ZOLADEX OR LHRH(3A)(AGONIST# OR ANTAGONIST#))

=> s (raloxifen# or droloxifen or centchroman)

L3 804 (RALOXIFEN# OR DROLOXIFEN OR CENTCHROMAN)

=> s l2 and l3

L4 17 L2 AND L3

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5 17 DUP REM L4 (0 DUPLICATES REMOVED)

=> s l5 and gynecolog?

L6 1 L5 AND GYNECOLOG?

=> d l6 abs ibib kwic 1

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2000 ACS
AB Combinations of LH-RH analogs and antiestrogens with tissue-selective estrogenic activity are useful for treatment of gynecol. disorders, esp. endometriosis and myomas. Thus, in rats with i.p. implants of endometrium as a model of endometriosis, the LH-RH antagonist **antide** (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to a redn. in endogenous estrogen level resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen **raloxifen** (3 mg/day orally) was also administered during the period of **antide** administration, the endometriosis regressed but no decrease in estrogen level occurred.
ACCESSION NUMBER: 1997:543582 CAPLUS
DOCUMENT NUMBER: 127:140580
TITLE: Combination of LH-RH analogs and antiestrogens for treatment of **gynecological** disorders
INVENTOR(S): Stoeckemann, Klaus; Muhn, Peter
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 5 pp.

CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19604231	A1	19970731	DE 1996-19604231	19960129
WO 9727863	A1	19970807	WO 1997-EP395	19970129
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9715969	A1	19970822	AU 1997-15969	19970129
EP 877621	A1	19981118	EP 1997-902258	19970129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1209750	A	19990303	CN 1997-191940	19970129
BR 9707210	A	19990406	BR 1997-7210	19970129
JP 2000505422	T2	20000509	JP 1997-527295	19970129
NO 9803465	A	19980918	NO 1998-3465	19980728
PRIORITY APPLN. INFO.:			DE 1996-19604231	19960129
			WO 1997-EP395	19970129

TI Combination of LH-RH analogs and antiestrogens for treatment of **gynecological** disorders

AB . . . esp. endometriosis and myomas. Thus, in rats with i.p. implants of endometrium as a model of endometriosis, the LH-RH antagonist **antide** (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to. . . resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen **raloxifen** (3 mg/day orally) was also administered during the period of **antide** administration, the endometriosis regressed but no decrease in estrogen level occurred.

ST LHRH analog antiestrogen endometriosis treatment; **antide** **raloxifen** endometriosis treatment; myoma treatment LHRH analog antiestrogen; gynecol disorder LHRH analog antiestrogen

IT 9034-40-6D, LHRH, analogs 31477-60-8, **Centchroman** 53714-56-0, **Leuprorelin** 57982-77-1 65807-02-5, **Zoladex** 82413-20-5, Droloxifene 84449-90-1, **Raloxifene** 112568-12-4, **Antide** 120287-85-6, **Cetrorelix** 127932-90-5, **Ramorelix** 193147-32-9
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of LH-RH analogs and antiestrogens for treatment of gynecol. disorders)

=> d his

=> s l5 and py <=1997

L7 5 L5 AND PY <=1997

=> d l7 abs ibib kwic 1-5

L7 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2000 ACS

AB Combinations of LH-RH analogs and antiestrogens with tissue-selective estrogenic activity are useful for treatment of gynecol. disorders, esp. endometriosis and myomas. Thus, in rats with i.p. implants of endometrium as a model of endometriosis, the LH-RH antagonist **antide** (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to a redn. in endogenous estrogen level resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen **raloxifen** (3 mg/day orally) was also administered during the period of **antide** administration, the endometriosis regressed but no decrease in estrogen level occurred.

ACCESSION NUMBER: 1997:543582 CAPLUS
DOCUMENT NUMBER: 127:140580
TITLE: Combination of LH-RH analogs and antiestrogens for treatment of gynecological disorders
INVENTOR(S): Stoeckemann, Klaus; Muhn, Peter
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 5 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
DE 19604231	A1	19970731	DE 1996-19604231	19960129	<--
WO 9727863	A1	19970807	WO 1997-EP395	19970129	<--
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9715969	A1	19970822	AU 1997-15969	19970129	<--
EP 877621	A1	19981118	EP 1997-902258	19970129	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
CN 1209750	A	19990303	CN 1997-191940	19970129	
BR 9707210	A	19990406	BR 1997-7210	19970129	
JP 2000505422	T2	20000509	JP 1997-527295	19970129	
NO 9803465	A	19980918	NO 1998-3465	19980728	
PRIORITY APPLN. INFO.:			DE 1996-19604231	19960129	
			WO 1997-EP395	19970129	

Appl.

PI DE 19604231 A1 **19970731**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19604231	A1	19970731	DE 1996-19604231	19960129 <--
WO 9727863	A1	19970807	WO 1997-EP395	19970129 <--
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9715969	A1	19970822	AU 1997-15969	19970129 <--
EP 877621	A1	19981118	EP 1997-902258	19970129
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CN 1209750	A	19990303	CN 1997-191940	19970129
BR 9707210	A	19990406	BR 1997-7210	19970129
JP 2000505422	T2	20000509	JP 1997-527295	19970129
NO 9803465	A	19980918	NO 1998-3465	19980728

AB . . . esp. endometriosis and myomas. Thus, in rats with i.p. implants. of endometrium as a model of endometriosis, the LH-RH antagonist **antide** (0.5 mg s.c. every 3 days for 4 wk) produced complete regression of cystic foci of endometriosis, but simultaneously to. . . resembling that occurring after ovariectomy, with a decrease in bone d. and an increase in osteoclast activity. When the antiestrogen **raloxifen** (3 mg/day orally) was also administered during the period of **antide** administration, the endometriosis regressed but no decrease in estrogen level occurred.

ST LHRH analog antiestrogen endometriosis treatment; **antide** **raloxifen** endometriosis treatment; myoma treatment LHRH analog antiestrogen; gynecol disorder LHRH analog antiestrogen

IT 9034-40-6D, LHRH, analogs 31477-60-8, **Centchroman** 53714-56-0, **Leuprorelin** 57982-77-1 65807-02-5, **Zoladex** 82413-20-5, Droloxifene 84449-90-1, **Raloxifene** 112568-12-4, **Antide** 120287-85-6, **Cetrorelix** 127932-90-5, **Ramorelix** 193147-32-9
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of LH-RH analogs and antiestrogens for treatment of gynecol. disorders)

L7 ANSWER 2 OF 5 USPATFULL

AB A method of inhibiting sexual precocity comprising administering to a human in need thereof an effective amount of a compound having the formula ##STR1## wherein R.sup.1 and R.sup.3 are independently hydrogen,
--CH.sub.3, ##STR2## wherein Ar is optionally substituted phenyl; R.sup.2 is selected from the group consisting of pyrrolidine, hexamethyleneamino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:80284 USPATFULL	
TITLE:	Methods of Inhibiting sexual precocity	
INVENTOR(S):	Dodge, Jeffrey A., Indianapolis, IN, United States	
PATENT ASSIGNEE(S):	Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)	
	NUMBER	DATE
PATENT INFORMATION:	US 5552417	19960903 <--
APPLICATION INFO.:	US 1995-442707	19950517 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-171393, filed on 21	

Dec 1993, now patented, Pat. No. US 5451590
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Fay, Zohreh
LEGAL REPRESENTATIVE: Sales, James J.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 394
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5552417 19960903 <--
SUMM Currently, three principal agents have been used to treat true precocious puberty including medroxyprogesterone acetate, cyproterone acetate, and **LHRH agonists**. The former two agents reverse or stop secondary sexual characteristics but do not effect final height, particularly for girls. The. . . action of circulating estradiol on skeletal growth. Thus, these agents do not correct for the excessive amount of circulating estradiol. **LHRH agonists** are currently the therapy of choice for true precocious puberty and act to block the effects endogenous LHRH and functions. . .
DETD **Raloxifene**, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R.sup.1 and R.sup.3 are hydrogen and R.sup.2 is 1-piperidinyl, is a nuclear regulatory molecule.
Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and. . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, **raloxifene** does block the action of estrogen in some cells; however in other cell types, **raloxifene** activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, **raloxifene** has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which **raloxifene** displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the **raloxifene**-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although **raloxifene** and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. . .
DETD . . . to effectively treat or prevent sexual precocity, or symptoms thereof, It also may be advantageous to administor a progestin or **LHRH agonist** with a compound of formula 1.
DETD Examples of specific capsule formulations of **raloxifene**, that have been made include those shown below:
DETD

Formulation 2: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 3: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	5

Starch, NF 108
Starch flowable powder
225.3
Silicone fluid 350 centistokes
1.7

DETD

Formulation 4: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 5: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

CLM What is claimed is:
5. The method of claim 1 wherein said human is also administered a progestin or **LHRH agonist**.

L7 ANSWER 3 OF 5 USPATFULL
AB A method of inhibiting fertility in women comprising administering to a female human an effective amount of a compound having the formula ##STR1## and pharmaceutically acceptable salts and solvates thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	95:97033 USPATFULL		
TITLE:	Methods of inhibiting fertility in women		
INVENTOR(S):	Jones, Charles D., Indianapolis, IN, United States Tinsley, Frank C., Indianapolis, IN, United States		
PATENT ASSIGNEE(S):	Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)		
	NUMBER	DATE	
PATENT INFORMATION:	US 5462949	19951031	<--
APPLICATION INFO.:	US 1993-170945	19931221 (8)	
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Fay, Zohreh		
LEGAL REPRESENTATIVE:	Sales, James J.; Dahling, Gerald V.		
NUMBER OF CLAIMS:	2		
EXEMPLARY CLAIM:	1		
LINE COUNT:	385		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5462949 19951031 <--
SUMM . . . stages of development are immunological methods (vaccination) and methods involving the direct control of LHRH secretion from the pituitary by **LHRH agonists** or **antagonists**.
SUMM . . . women. The methods of treatment provided by this invention are practiced by administering to a female human a dose of **raloxifene** or a pharmaceutically acceptable salt or solvate

thereof, that is effective to inhibit fertility. The term inhibit fertility includes reducing. . .

SUMM **Raloxifene**, which is the hydrochloride salt of the compound of formula 1, has been shown to bind to the estrogen receptor. . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, **raloxifene** does block the action of estrogen in some cells; however in other cell types, **raloxifene** activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. The unique profile which **raloxifene** displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the **raloxifene**-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although **raloxifene** and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. . .

SUMM

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Raloxifene	0.1-1000
Starch, NF	0-650
Starch flowable powder	0-650
Silicone fluid 350 centistokes	0-15

DETD

Formulation 2: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 3: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 4: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

DETD

Formulation 5: **Raloxifene** capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

DETD

Formulation 6: Tablets

Ingredient	Quantity (mg/tablet)
Raloxifene	0.1-1000
Cellulose, microcrystalline	0-650
Silicon dioxide, fumed	0-650
Stearate acid	0-15

DETD

Formulation 7: Tablets

Ingredient	Quantity (mg/tablet)
Raloxifene	0.1-1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

DETD

Formulation 8: Suspensions

Ingredient	Quantity (mg/5 ml)	
Raloxifene	0.1-1000	mg
Sodium carboxymethyl cellulose	50	mg
Syrup	1.25	mg
Benzoic acid solution	0.10	mL
Flavor	q.v.	
Color	q.v.	
Purified water to	5	mL

DETD . . . of the groups serves as the control group and the other groups as experimental groups, each such experimental group receiving **raloxifene** at a particular dose level. **Raloxifene** is prepared in corn oil such that the daily administration is in 0.1 ml. of vehicle. The designated quantity of **raloxifene** in the vehicle is administered to each rat within the defined group subcutaneously (sc) daily. Alternatively, administration may be made. . . gavage or an intramuscular route. The control group receives only the vehicle. Administration of the vehicle or the combination of **raloxifene**

and vehicle is continued on a daily basis for 15 days. On the 5th day of
treatment, one or two. . .

DETD The male rats are removed, and the experimental groups of female rats are administered **raloxifene** via oral garage, an intramuscular route, or by subcutaneous injection. The administration continues on a daily basis until the twelfth. . .

L7 ANSWER 4 OF 5 USPATFULL

AB A method of inhibiting sexual precocity comprising administering to a human in need thereof an effective amount of a compound having the formula ##STR1## wherein R.sup.1 and R.sup.3 are independently hydrogen,
--CH.sub.3, ##STR2## wherein Ar is optionally substituted phenyl; R.sup.2 is selected from the group consisting of pyrrolidine, hexamethyleneamino, and piperidino; or a pharmaceutically acceptable salt of solvate thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	95:84387 USPATFULL	
TITLE:	Methods of inhibiting sexual precocity	
INVENTOR(S):	Dodge, Jeffrey A., Indianapolis, IN, United States	
PATENT ASSIGNEE(S):	Eli Lilly & Co., Indianapolis, IN, United States (U.S. corporation)	

	NUMBER	DATE	
PATENT INFORMATION:	US 5451590	19950919	<--
APPLICATION INFO.:	US 1993-171393	19931221 (8)	

DOCUMENT TYPE:	Utility
PRIMARY EXAMINER:	Fay, Zohreh
LEGAL REPRESENTATIVE:	Sales, James J.; Dahling, Gerald V.
NUMBER OF CLAIMS:	5
EXEMPLARY CLAIM:	1
LINE COUNT:	383

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5451590 19950919 <--

SUMM Currently, three principal agents have been used to treat true precocious puberty including medroxyprogesterone acetate, cyproterone acetate, and **LHRH agonists**. The former two agents reverse or stop secondary sexual characteristics but do not effect final
height, particularly for girls. The. . . action of circulating estradiol on skeletal growth. Thus, these agents do not correct for the excessive amount of circulating estradiol. **LHRH agonists** are currently the therapy of choice for true precocious puberty and act to block the effects endogenous LHRH and functions. . .

DETD **Raloxifene**, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R.sup.1 and R.sup.3 are hydrogen and R.sup.2 is 1-piperidinyl, is a nuclear regulatory molecule.
Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and. . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, **raloxifene** does block the action of estrogen in some cells; however in other cell types, **raloxifene** activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, **raloxifene** has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which **raloxifene** displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the

raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although **raloxifene** and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. . .

DETD . . . to effectively treat or prevent sexual precocity, or symptoms thereof. It also may be advantageous to administor a progestin or **LHRH agonist** with a compound of formula 1.

DETD Examples of specific capsule formulations of **raloxifene**, that have been made include those shown below:

DETD

Ingredient	Quantity (mg/capsule)
Formulation 2: **Raloxifene** capsule	
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7
Formulation 3: **Raloxifene** capsule	
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7
Formulation 4: **Raloxifene** capsule	
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7
Formulation 5: **Raloxifene** capsule	
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

CLM What is claimed is:

5. The method of claim 1 wherein said human is also administered a progestin or **LHRH agonist**.

L7 ANSWER 5 OF 5 USPATFULL

AB A method of inhibiting ovarian dysgenesis, delayed puberty, or sexual infantilism comprising administering to a human in need thereof an effective amount of a compound having the formula ##STR1## wherein R.sup.1 and R.sup.3 are independently hydrogen, --CH.sub.3, ##STR2## wherein Ar is optionally substituted phenyl; R.sup.2 is selected from the group consisting of pyrrolidine, hexamethyleneamino, and piperidino;

or a pharmaceutically acceptable salt of solvate thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 95:84386 USPATFULL

TITLE: Methods of inhibiting ovarian dysgenesis, delayed puberty, or sexual infantilism

INVENTOR(S): Dodge, Jeffrey A., Indianapolis, IN, United States

PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5451589	19950919	<--
APPLICATION INFO.:	US 1993-170946	19931221 (8)	

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Fay, Zohreh
LEGAL REPRESENTATIVE: Sales, James J.; Dahling, Gerald V.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 385
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5451589 19950919 <--
DETD **Raloxifene**, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R.sup.1 and R.sup.3 are hydrogen and R.sup.2 is 1-piperidinyl, is a nuclear regulatory molecule.

Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and. . . an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, **raloxifene** does block the action of estrogen in some cells; however in other cell types, **raloxifene** activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, **raloxifene** has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which **raloxifene** displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the **raloxifene**-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although **raloxifene** and estrogen utilize and compete for the same receptor, the pharmacological outcome from gene regulation of the two is not. . .

DETD . . . or sexual infantilism, or symptoms thereof. Also, other active ingredients may be administered to a human in need, such as **LHRH agonists** or progestins.

DETD Examples of specific capsule formulations of **raloxifene**, that have been made include those shown below:

DETD

Ingredient	Quantity (mg/capsule)
Formulation 2: **Raloxifene** capsule	
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7
Formulation 3: **Raloxifene** capsule	
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7
Formulation 4: **Raloxifene** capsule	
Raloxifene	10
Starch, NF	103
Starch flowable powder	

225.3
Silicone fluid 350 centistokes
1.7
Formulation 5: **Raloxifene** capsule
Raloxifene 50
Starch, NF 150
Starch flowable powder
397
Silicone fluid 350 centistokes
3.0

=> s lhrh(3a)(agonist# or antagonist#)) and (antiestrogen# or anti(w)estrogen# or anti-oestrogen# or antioestrogen#)

UNMATCHED RIGHT PARENTHESIS 'TAGONIST#)) AND'
The number of right parentheses in a query must be equal to the number of left parentheses.

=> s lhrh(3a)(agonist# or antagonist#) and (antiestrogen# or anti(w)estrogen# or anti-oestrogen# or antioestrogen#)

L8 69 LHRH(3A)(AGONIST# OR ANTAGONIST#) AND (ANTIESTROGEN# OR ANTI(W)
ESTROGEN# OR ANTI-OESTROGEN# OR ANTIOESTROGEN#)

=> s l8 and (gynecolog? or endometrios? or myoma##)

L9 34 L8 AND (GYNECOLOG? OR ENDOMETRIOS? OR MYOMA##)

=> dup rem l9

PROCESSING COMPLETED FOR L9
L10 34 DUP REM L9 (0 DUPLICATES REMOVED)

=> s l10 and py<=1996

L11 10 L10 AND PY<=1996

=> d l11 abs ibib kwic 1-10

L11 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2000 ACS
AB Since uterine leiomyomata (fibroids) are not found in conditions where estradiol is either absent or present only in low concns., estradiol is considered to be an important factor in the control of fibroid growth. To detn. whether this is due to a direct effect on the tissue, estradiol and progesterone receptors were measured in tissue removed at hysterectomy from normally cycling women, women who had received the gonadotropin-releasing hormone (GnRH) agonist Zoladex (ICI 118630) as a s.c. depot given at monthly intervals for 3 mo preoperatively, and women who had received the **antiestrogen** tamoxifen (20 mg daily) for 3 mo before surgery. Both unoccupied estradiol receptors (measured by sepg. bound from free hormone with dextran-coated charcoal) and total receptor populations (as measured by an enzyme immunoassay) were measured in each fibroid and adjoining myometrium. There was more binding of both estradiol and progestogen to fibroid than to myometrium in both the control and agonist-treated groups. Estradiol binding to fibroids in women treated with Zoladex exceeded that in the normally cycling women which in turn exceeded that in the tamoxifen-treated group. However, the binding of progestogen, measured by dextran-coated charcoal, showed the

reverse trend. These results may be explained by the low circulating estradiol concn. in the GnRH agonist-treated women, leading to low receptor occupancy.

ACCESSION NUMBER: 1989:206008 CAPLUS
DOCUMENT NUMBER: 110:206008
TITLE: The binding of steroids to myometrium and leiomyomata (fibroids) in women treated with the gonadotropin-releasing hormone agonist Zoladex (ICI 118630)
AUTHOR(S): Lumsden, M. A.; West, C. P.; Hawkins, R. A.; Bramley, T. A.; Rumgay, L.; Baird, D. T.
CORPORATE SOURCE: Cent. Reprod. Biol., Univ. Edinburgh, Edinburgh, EH3 9EW, UK
SOURCE: J. Endocrinol. (**1989**), 121(2), 389-96
CODEN: JOENAK; ISSN: 0022-0795
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Endocrinol. (**1989**), 121(2), 389-96
CODEN: JOENAK; ISSN: 0022-0795
AB . . . (ICI 118630) as a s.c. depot given at monthly intervals for 3 mo preoperatively, and women who had received the **antiestrogen** tamoxifen (20 mg daily) for 3 mo before surgery. Both unoccupied estradiol receptors (measured by sepg. bound from free hormone. . .
ST leiomyomata steroid receptor; **LHRH agonist** uterus steroid receptor
IT **Myoma**
(leio-, estradiol and progestogen receptors of, in women, gonadotropin-releasing hormone agonist effect on)

L11 ANSWER 2 OF 10 USPATFULL
AB Certain steroidal and non-steroidal compounds have been found to inhibit androgen and estrogen formation. Such inhibition may aid in the reduction of the activity of these hormones and may be useful in the treatment of diseases where, for example, inhibition of androgen or estrogen activity is desired. Preferred inhibitors also possess antiestrogenic activity, thus providing the advantage of a double inhibitory action both on estrogen formation and on estrogen action (blockade of estrogen receptors by antiestrogenic action).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 96:116412 USPATFULL
TITLE: Inhibitors of sex steroid biosynthesis and methods for their production and use
INVENTOR(S): Labrie, Fernand, Ste.-Foy, Canada
Merand, Yves, Ste.-Foy, Canada
PATENT ASSIGNEE(S): Endorecherche Inc., Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5585405	19961217	<--
APPLICATION INFO.:	US 1994-283989	19940801 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1992-966112, filed on 22 Oct 1992, now patented, Pat. No. US 5364847 which is a continuation of Ser. No. US 1989-322154, filed on 10 Mar 1989, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Jordan, Kimberly
LEGAL REPRESENTATIVE: Ostrolenk, Faber, Gerb & Soffen, LLP
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1357
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5585405 19961217 <--
DETD . . . sex steroid formation and to act as antagonists to sex steroid activity by blocking sex steroid receptors. For example, preferred **antiestrogens** which also act as inhibitors of estrogen formation include, but are not limited to, N-butyl, N-methyl-11-(16.alpha.-chloro-3', 17'.beta.-dihydroxy estra-1',3',5'(10')-trien-7'.alpha.-yl) undecanamide ("EM. . . are not limited to, malignant as well as non-malignant steroid-sensitive diseases, especially breast cancer, prostate cancer, ovarian cancer, endometrial cancer, **endometriosis**, uterine leiomyomata, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia benign prostatic hyperplasia, sexual deviants as well as for male and. . . at a step preceeding steroid receptors, thus acting prior to and in addition to the action of steroid antagonists (e.g. **antiestrogens** or antiandrogens).

DETD Such compounds administered at appropriate doses are of value in all conditions where **antiestrogens** and antiandrogens are beneficial. In particular this approach is of value in breast cancer, prostate cancer, endometrial cancer, ovarian cancer, **endometriosis**, benign prostatic hyperplasia, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia, menstrual disorders and as male and female contraceptive as well. . .

DETD . . . dosage of the above-described compound (multi sex hormone blocker) are the same as in intact patients or patients receiving an **LHRH agonist** or **antagonist**.

DETD The composition may contain, in addition to the steroid and/or nonsteroidal derivatives of the invention, other **antiestrogens** and/or antiandrogens and/or enzymatic inhibitors and/or inhibitors of ACTH and/or growth hormone and/or prolactin secretion.

DETD . . . phase was washed with water, dried on anhydrous Na.sub.2 SO.sub.4 and evaporated under reduced pressure. The residue included two important **antiestrogens** which were separated by chromatography on silica gel and eluted with a mixture of EtOAc/hexane (4:6 v/v) to give: N-butyl,. . .

L11 ANSWER 3 OF 10 USPATFULL

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:97032 USPATFULL
TITLE:	Methods for preventing and treating osteoporosis with low dose non-masculinizing androgenic compounds
INVENTOR(S):	Labrie, Fernand, Quebec, Canada
PATENT ASSIGNEE(S):	Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)

	NUMBER	DATE	
PATENT INFORMATION:	US 5567695	19961022	<--
APPLICATION INFO.:	US 1995-483761	19950607 (8)	

RELATED APPLN. INFO.: Division of Ser. No. US 1994-282964, filed on 29 Jul 1994 which is a division of Ser. No. US 1993-15083, filed on 8 Feb 1993, now patented, Pat. No. US 5362720 which is a continuation of Ser. No. US 1991-724532,

filed on 28 Jun 1991, now abandoned
DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Nutter, Nathan M.
LEGAL REPRESENTATIVE: Ostrolenk, Faber, Gerb & Soffen, LLP
NUMBER OF CLAIMS: 29
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1453
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5567695 19961022 <--
AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and. . .
SUMM This invention relates to a method for treating or preventing breast and endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . .
SUMM . . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already developed breast cancer are related to the inhibition of estrogen action and/or. . .
SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . .
SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20:1381, 1984; Manni et al., Endocr. Rev. 7:89-94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23:843-848, 1985).
SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.
SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.
SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.
SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.
SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.
SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means

(use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]**LHRH** ethylamide, or **antagonists**) as part of a combination therapy. **Antiestrogens**, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa.. . .

SUMM . . . ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . 40% in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27:447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50:743, 1987; Preston, Obstet, Gynecol. 2:152, 1965). Androgenic and masculinizing side effects (sometimes irreversible) are however. . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . of said androgenic steroid described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for all purposes which are enhanced by administering androgens or otherwise. . .

DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms assodated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . .

DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .

DETD . . . the above therapy using the described regimen, tumor growth of

breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 4 OF 10 USPATFULL

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose. Of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:72882 USPATFULL	
TITLE:	Activation of androgen receptors with low dose non-masculinizing androgenic compounds	
INVENTOR(S):	Labrie, Fernand, Quebec, Canada	
PATENT ASSIGNEE(S):	Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)	
	NUMBER	DATE
PATENT INFORMATION:	US 5545634	19960813 <--
APPLICATION INFO.:	US 1994-282964	19940729 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1993-15083, filed on 8 Feb 1993, now patented, Pat. No. US 5362720 which is a continuation of Ser. No. US 1991-724532, filed on 28 Jun 1991, now abandoned	
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Nutter, Nathan M.	
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen, LLP	
NUMBER OF CLAIMS:	11	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)	
LINE COUNT:	1406	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5545634 19960813 <--

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose. Of a progestin or other steroid derivative having androgenic activity and. . .

SUMM This invention relates to a method for treating or preventing breast and endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . .

SUMM . . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already developed breast cancer are related to the inhibition of estrogen action and/or. . .

SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum

estrogens to castrated levels. . .

SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984; Manni et al., Endocr. Rev. 7: 89,-94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23: 843-848, 1985).

SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.

SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.

SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.

SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.

SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.

SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means (use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]**LHRH** ethylamide, or **antagonists**) as part of a combination therapy. **Antiestrogens**, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa.. . .

SUMM . . . ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27: 447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet, Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects

on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . of said androgenic steroid described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for all purposes which are enhanced by administering androgens or otherwise. . .

DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . .

DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .

DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 5 OF 10 USPATFULL

AB Methods of treatment and prevention of estrogen-related diseases, and of fertility control, include low dose (e.g. less than 50 nanomolar serum concentration) administration of certain anabolic steroids, progestins and other substantially non-masculinizing androgenic compounds. Sustained release formulations substantially free of organic solvent, and sustained release formulations for maintaining low serum levels of androgen are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	96:67992 USPATFULL	
TITLE:	Controlled release systems and low dose androgens	
INVENTOR(S):	Labrie, Fernand, Quebec, Canada Lepage, Martin, Quebec, Canada	
PATENT ASSIGNEE(S):	Endorecherche, Inc., Canada (non-U.S. corporation)	
	NUMBER	DATE
PATENT INFORMATION:	US 5541172	19960730 <--
APPLICATION INFO.:	US 1995-474347	19950607 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1995-398096, filed on 3 Mar 1995 which is a division of Ser. No. US 1992-900817, filed on 24 Jun 1992 which is a continuation-in-part of Ser. No. US 1991-724532, filed on 28 Jun 1991	
DOCUMENT TYPE:	Utility	

PRIMARY EXAMINER: Nutter, Nathan M.
LEGAL REPRESENTATIVE: Ostrolenk, Faber, Gerb & Soffen
NUMBER OF CLAIMS: 1
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Figure(s); 13 Drawing Page(s)
LINE COUNT: 2236
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5541172 19960730 <--
SUMM This invention relates to a method for treating or preventing breast and endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . .
SUMM . . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already developed breast cancer are related to the inhibition of estrogen action and/or. . .
SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . .
SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984;. . .
SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.
SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.
SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.
SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.
SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.
SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means (use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]**LHRH** ethylamide, or **antagonists**) as part of a combination therapy. **Antiestrogens**, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .
SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did

not respond to Tamoxifen could respond to Fluoxymesterone and vice versa.. . .

SUMM . . . ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27: 447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . .

SUMM . . . et al., Am. J. Obstet. Gynecol. 158: 797-807, 1988). The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet. Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet, Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . activities induced by estrogens. For example, estrogen-related diseases include but are not limited to breast cancer, endometrial cancer, bone loss, **endometriosis** and osteoporosis.

SUMM The methods described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for other purposes which are enhanced by administering androgens or otherwise. . .

SUMM . . . for treating or preventing estrogen sensitive diseases and disorders including but not limited to breast cancer, endometrial cancer, osteoporosis and **endometriosis**. The methods comprise administering to a patient in need of such treatment or prevention, an effective amount of sustained release. . .

DETD . . . not only for their more rational use in the prevention and therapy of breast and endometrial cancers as well as **endometriosis** and bone loss but also to avoid side effects caused by interaction with steroid receptors unnecessary for the desired beneficial. . .

DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . .

DETD . . . prevent other signs and symptoms of menopause. In women, when

estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .

DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 6 OF 10 USPATFULL

AB Methods of treatment and prevention of estrogen-related diseases, and of fertility control, include low dose (e.g. less than 50 nanomolaR serum concentration) administration of certain anabolic steroids, progestins and other substantially non-masculinizing androgenic compounds. Sustained release formulations substantially free of organic solvent, and sustained release formulations for maintaining low serum levels of androgen are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	95:64916 USPATFULL	
TITLE:	Controlled release systems and low dose androgens	
INVENTOR(S):	Labrie, Fernand, Quebec, Canada Lepage, Martin, Quebec, Canada	
PATENT ASSIGNEE(S):	Endorecherche, Inc., Quebec, Canada (non-U.S. corporation)	
	NUMBER	DATE
PATENT INFORMATION:	US 5434146	19950718 <--
APPLICATION INFO.:	US 1992-900817	19920624 (7)
DISCLAIMER DATE:	20111108	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1991-724532, filed on 28 Jun 1991, now abandoned	
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Nutter, Nathan M.	
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen	
NUMBER OF CLAIMS:	16	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	15 Drawing Figure(s); 9 Drawing Page(s)	
LINE COUNT:	2424	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5434146 19950718 <--

SUMM This invention relates to a method for treating or preventing breast and endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . .

SUMM . . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already breast cancer are related to the inhibition of estrogen action and/or formation.. . .

SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing

Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . .

SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984; Manni et al., Endocr. Rev. 7: 89-94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23: 843-848, 1985).

SUMM U.S. Pat. No. 4,071,622 relates to the use of certain **LHRH agonists** against DMBA-induced mammary carcinoma in rats.

SUMM . . . relates to the treatment of female breast cancer by use of a combination therapy comprising administering an antiandrogen and an **antiestrogen** to a female after the hormone output of her ovaries has been blocked by chemical or surgical means.

SUMM . . . No. 4,760,053 describes a treatment of selected sex steroid dependent cancers which includes various specified combinations of compounds selected from **LHRH agonists**, antiandrogens, **antiestrogens** and certain inhibitors of sex steroid biosynthesis.

SUMM . . . 4,472,382 relates to treatment of prostatic adenocarcinoma, benign prostatic hypertrophy and hormone-dependent mammary tumors with specified pharmaceuticals or combinations. Various **LHRH agonists** and antiandrogens are discussed.

SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.

SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means (use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]**LHRH** ethylamide, or **antagonists**) as part of a combination therapy.

Antiestrogens, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa.. . .

SUMM . . . ZR-75-1 human breast carcinoma cells in inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo. . .

SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.

SUMM . . . in unselected breast cancer patients (Horwitz, J. Steroid Biochem. 27: 447-457, 1987), an efficacy comparable to that of the non-steroidal **antiestrogen** tamoxifen (Lippman, Semin. Oncol. 10 (Suppl.): 11-19, 1983). Its more general use, however, is for breast cancer relapsing after other. . .

SUMM . . . et al., Am. J. Obstet. Gynecol, 158: 797-807, 1988). The androgen methyltesiosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet. Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . .

SUMM The androgen methyltestosterone has been shown to relieve the symptoms of **endometriosis** (Hamblen, South Med. J. 50: 743, 1987; Preston, Obstet. Gynecol. 2: 152, 1965). Androgenic and masculinizing side effects (sometimes irreversible). . .

SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirble deleterious effects on bone mass in women.

SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.

SUMM . . . activities induced by estrogens. For example, estrogen-related diseases include but are not limited to breast cancer, endometrial cancer, bone loss, **endometriosis** and osteoporosis.

SUMM The methods described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for other purposes which are enhanced by administering androgens or otherwise. . .

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DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . .

DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . .

DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .

DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .

DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 7 OF 10 USPATFULL

AB Inhibitors of sex steroid activity, for example those having the general structure ##STR1## may be used as part of a pharmaceutical composition to provide antiestrogenic effects and/or to suppress estrogen synthesis.

Such pharmaceutical compositions are useful for the treatment of breast cancer or other diseases whose progress is aided by activation of sex steroid receptors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	95:20734 USPATFULL	
TITLE:	Anti-estrogenic compounds and compositions	
INVENTOR(S):	Labrie, Fernand, Quebec, Canada Merand, Yves, Quebec, Canada	
PATENT ASSIGNEE(S):	Endorecherche Inc., Canada (non-U.S. corporation)	
	NUMBER	DATE
PATENT INFORMATION:	US 5395842	19950307 <--
APPLICATION INFO.:	US 1991-801704	19911202 (7)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1988-265150, filed on 31 Oct 1988, now abandoned And a continuation-in-part of Ser. No. US 1989-377010, filed on 7 Jul 1989, now abandoned	
DOCUMENT TYPE:	Utility	
PRIMARY EXAMINER:	Cintins, Marianne M.	
ASSISTANT EXAMINER:	Criares, T. J.	
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen	
NUMBER OF CLAIMS:	66	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)	
LINE COUNT:	3525	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5395842 19950307 <--

SUMM This invention relates to novel inhibitors of sex steroid activity such as **antiestrogen** compounds having effective antagonistic capability while substantially lacking agonistic effects. More particularly, certain preferred embodiments of the invention relate to. . .

SUMM . . . the amount of sex steroid available to act at these sites. For example, alternative or concurrent therapy to administration of **antiestrogens** could involve attempts to block the production of estrogens (e.g. by ovariectomy) such that less is available to activate receptor. . .

SUMM There is, therefore, a need in the art for **antiestrogens** which effectively block estrogen receptors with minimal or no agonistic effect. In Wakeling and Bowler, "Steroidal Pure **Antioestrogens** ", J. Endocrinol. 112:R7-R10 (1987), a steroid derivative is said to act as an **antiestrogen** but to exhibit some estrogen activity. The net effectiveness of a compound is effected by both its agonistic (undesirable) and. . .

SUMM In U.S. Pat. No. 4,094,994, it is disclosed that the use of certain **antiestrogens** may inhibit certain human breast tumor cells.

SUMM H. Mouridsen et al., Cancer Treatm. Rev.,5: 131-141 (1978), discloses that Tamoxifen, an **antiestrogen**, is effective in remission of advanced breast cancer in about 30 percent of the women patients treated.

SUMM The combined use of the **antiestrogen** Tamoxifen and a luteinizing hormone-releasing hormone agonist, Buserelin, is also known for treatment of breast cancer. See, for instance, Klijn. . .

SUMM . . . male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g., by use of an **LHRH agonist**, e.g., [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]LHRH ethylamide. The treatment includes administering an antiandrogen, e.g., flutamide in association with at least one inhibitor. . .

SUMM U.S. Pat. No. 4,472,382 relates to a method of treating prostate cancer

using the combination of an antiandrogen and an **LHRH agonist**.

SUMM Von Angerer et al. discuss other **antiestrogens** in "1-(aminoalkyl)-2-phenylindoles as Novel Pure Estrogen Antagonists", J. Med. Chem. 1990; 33: 2635-2640. In U.S. Pat. No. 4,094,994, where it is said that the use of certain **antiestrogens** inhibit certain human breast tumor cells. See also DE 3821148.

SUMM . . . et al., J. Med. Chem. 33: 3216-3222 and 3222-3229 (1990) described the synthesis and biological activities of 2,3-diaryl-2H-1-benzopyrans analogs as **antiestrogens** having the following molecular structure: ##STR2##

SUMM . . . et al., J. Med. Chem. 32: 1700-1707 (1989) describe the synthesis and biological activities of benzofuran and triarylfuran analogues as **antiestrogens**.

SUMM It is another object of the invention to provide a pure **antiestrogen** for therapeutic use.

SUMM It is another object to provide an **antiestrogen** having good affinity for estrogen receptors, but substantially lacking undesirable agonistic activity regarding these receptors and substantially lacking hormonal activity.

SUMM . . . in the treatment of estrogen-related diseases. These diseases include, but are not limited to breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

SUMM . . . of inhibiting the activity of androgens and estrogens, respectively. For example, estrogen activity inhibitors include, but are not limited to **antiestrogens** which block estrogen receptors, thereby making them unavailable to estrogen compounds which could otherwise activate those receptors. Sex steroid activity. . .

DRWD . . . affinity of estradiol, diethylstilbestrol, ICI 164384 (Wakeling, A. E. and Bowler, J., 1987; J. Endocrinol. 112: R7-R110) and EM-142 (an **antiestrogen** having a nonsteroidal nucleus and synthesized in example 1, herein) for the rat uterine cytosol receptor (Asselin et al., 1978;. . .

DRWD FIG. 3 is a graph illustrating the antiestrogenic activity of another **antiestrogen** EM 139.

DRWD FIG. 4 is a graph illustrating that the **antiestrogen** which is the subject of FIG. 3 is also a good inhibitor of sex steroid synthesis.

DRWD FIG. 5 is a graph illustrating the **antiestrogen** activity of EM 343 and EM 312, other sex steroid inhibitors of the invention.

DETD When administered systemically, pharmaceuticals of the inventions may be used in the treatment of breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

DETD Pharmaceutical compositions comprise therapeutically effective amounts of one or more of the sex steroid activity inhibitors (including **antiestrogens**) discussed herein wherein a pharmaceutically acceptable diluent or carrier is included with the active compound(s). The diluent or carrier will. . .

DETD A composition suitable for parenteral administration preferably contains a carrier and an **antiestrogen** in accordance with the invention at a concentration sufficient to introduce from about 1 mg to about 1000 (preferably 5 to 50) mg of the **antiestrogen** per 50 kg of body weight per day. The volume flow will, of course, vary with the concentration at which. . .

DETD After E.sub.2 and/or **antiestrogen** treatment, cells were harvested by addition of 0.5 ml of a pancreatin solution (Sigma) for 5-10 min at 37.degree. C.. . .

DETD Set forth below are some flow charm description and illustration of a

number of preferred synthesis schemes for certain preferred **antiestrogens** in accordance with the invention. The steps set forth below are set forth merely by way of example. Those of skill in the art will readily recognize alternative synthetic pathways and variations capable of producing a variety of **antiestrogens** and other sex steroid activity inhibitors in accordance with the invention.

DETD EFFECTIVENESS OF **ANTIESTROGEN** SYNTHESIZED IN EXAMPLE 1

DETD . . . can be seen that EM-142 is only 3 times less potent than 17.beta.-estradiol itself while being more potent than the **antiestrogen** ICI 164384.

DETD EFFICACY OF AN **ANTIESTROGEN** SYNTHESIZED IN ACCORDANCE WITH EXAMPLE 9

DETD . . . Scheme 9 above is an estrogen activity inhibitor. "EM 139" has been tested both for efficacy in acting as an **antiestrogen** by blocking estrogen receptors without substantially activating those receptors (see FIG. 3), and for efficacy in inhibiting 17.beta.-hydroxysteroid dehydrogenase (see. . .

L11 ANSWER 8 OF 10 USPATFULL

AB Certain steroidal and non-steroidal compounds have been found to inhibit androgen and estrogen formation. Such inhibition may aid in the reduction of the activity of these hormones and may be useful in the treatment of diseases where, for example, inhibition of androgen or estrogen acitivity is desired. Preferred inhibitors also possess antiestrogenic activity, thus providing the advantage of a double inhibitory action both on estrogen formation and on estrogen action.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	94:99900 USPATFULL	
TITLE:	Inhibitors of sex steroid biosynthesis and methods for their production and use	
INVENTOR(S):	Labrie, Fernand, Quebec, Canada Merand, Yves, Quebec, Canada	
PATENT ASSIGNEE(S):	Endorecherche, Canada (non-U.S. corporation)	

	NUMBER	DATE	
PATENT INFORMATION:	US 5364847	19941115	<--
APPLICATION INFO.:	US 1992-966112	19921022 (7)	

DISCLAIMER DATE:	20100420
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1989-322154, filed on 10 Mar 1989, now abandoned
DOCUMENT TYPE:	Utility
PRIMARY EXAMINER:	Cintins, Marianne M.
ASSISTANT EXAMINER:	Jordan, Kimberly R.
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen
NUMBER OF CLAIMS:	11
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT:	1504

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5364847 19941115 <--

DETD . . . sex steroid formation and to act as antagonists to sex steroid activity by blocking sex steroid receptors. For example, preferred **antiestrogens** which also act as inhibitors of estrogen formation include, but are not limted to, N-butyl, N-methyl-11-(16.alpha.-chloro-3',17'.beta.-dihydroxy estra-1',3',5'(10')-trien-7'.alpha.-yl) undecanamide ("EM 139"),. . . are not limited to, malignant as well as non-malignant steroid-sensitive diseases, especially brease cancer, prostate cancer, ovarian cancer, endometrial cancer, **endometriosis**, uterine leiomyomata, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia, benign prostatic hyperplasia, sexual deviants as well as for male and. . . at a step

preceeding steroid receptors, thus acting prior to and in addition to the action of steroid antagonists (e.g. **antiestrogens** or antiandrogens).

DETD Such compounds administered at appropriate doses are of value in all conditions where **antiestrogens** and antiandrogens are beneficial. In particular, this approach is of value in breast cancer, prostate cancer, endometrial cancer, ovarian cancer, **endometriosis**, benign prostatic hyperplasia, precocious puberty, hirsutism, acne, seborrhea, androgenic alopecia, menstrual disorders and as male and female contraceptive as well. . .

DETD . . . dosage of the above-described compound (multi sex hormone blocker) are the same as in intact patients or patients receiving an **LHRH agonist** or **antagonist**.

DETD The composition may contain, in addition to the storoid and/or nonsteroidal derivatives of the invention, other **antiestrogens** and/or antiandrogens and/or enzymatic inhibitors and/or inhibitors of ACTH and/or growth hormone and/or prolactin secretion.

DETD . . . phase was washed with water, dried on anhydrous Na.sub.2 SO.sub.4 and evaporated under reduced pressure. The residue included two important **antiestrogens** which were separated by chromatography on silica gel and eluted with a mixture of EtOAc/hexane (4:6 v/v) to give: N-butyl,. . .

L11 ANSWER 9 OF 10 USPATFULL

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and low masculinizing activity. Pharmaceutical compositions useful for such treatment and pharmaceutical kits containing such compositions are disclosed. An in vitro assay permitting specific measurements of androgenic activity of potentially useful compounds is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	94:97559 USPATFULL		
TITLE:	Methods of treating or preventing breast or endometrial cancer with low dose non-masculinizing androgenic compounds		
INVENTOR(S):	Labrie, Fernand, Quebec, Canada		
PATENT ASSIGNEE(S):	Endorecherche, Inc., Canada (non-U.S. corporation)		
	NUMBER	DATE	
PATENT INFORMATION:	US 5362720	19941108	<--
APPLICATION INFO.:	US 1993-15083	19930208 (8)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1991-724532, filed on 28 Jun 1991, now abandoned		
DOCUMENT TYPE:	Utility		
PRIMARY EXAMINER:	Nutter, Nathan M.		
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen		
NUMBER OF CLAIMS:	30		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	1452		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5362720 19941108 <--

AB A method of treatment or prevention of breast and endometrial cancer, osteoporosis and **endometriosis** in susceptible warm-blooded animals comprising administering a low dose of a progestin or other steroid derivative having androgenic activity and. . .

SUMM This invention relates to a method for treating or preventing breast and

endometrial cancer, bone loss, and for treating **endometriosis** in susceptible warm-blooded animals including humans involving administration of a compound possessing androgenic activity, and to kits containing active ingredients. . .

SUMM . . . for breast and endometrial cancer as well as for the prevention and treatment of bone loss and for treatment of **endometriosis**. The main approaches for the treatment of already developed breast cancer are related to the inhibition of estrogen action and/or. . .

SUMM . . . irradiation, two procedures giving irreversible castration. Recently, a reversible form of castration has been achieved by utilizing Luteinizing Hormone-Releasing Hormone **Agonists** (**LHRH agonists**) which, following inhibition of secretion of bioactive Luteinizing Hormone (LH) by the pituitary gland, decrease serum estrogens to castrated levels. . .

SUMM Several studies show that treatment of premenopausal breast cancer patients with **LHRH agonists** induces responses comparable to those achieved with other forms of castration (Klijn et al., J. Steroid Biochem. 20: 1381, 1984; Manni et al., Endocr. Rev. 7: 89=94, 1986). Beneficial effects of treatment with **LHRH agonists** have also been observed in postmenopausal women (Nicholson et al., J. Steroid Biochem. 23: 843-848, 1985).

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SUMM . . . discloses a method of treating sex steroid dependent cancers in warm-blooded animals which comprises administering specific pharmaceuticals and combinations. Antiandrogens, **antiestrogens**, certain inhibitors of sex steroid biosynthesis and blocking of hormonal output are discussed.

SUMM . . . warm-blooded animals which may include inhibition of ovarian hormonal secretion by surgical means (ovariectomy) or chemical means (use of an **LHRH agonist**, e.g. [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]**LHRH** ethylamide, or **antagonists**) as part of a combination therapy. **Antiestrogens**, androgens, progestins, inhibitors of sex steroid formation (especially of 17.beta.-hydroxysteroid dehydrogenase- or aromatase-catalyzed production of sex steroids), inhibitors of prolactin. . .

SUMM The independent beneficial effect of an androgen combined with an **antiestrogen** is suggested by the report that patients who did not respond to Tamoxifen could respond to Fluoxymesterone and vice versa.. . .

SUMM . . . ZR-75-1 human breast carcinoma cells is inhibited by androgens, the inhibitory effect of androgens being additive to that of an **antiestrogen**. The inhibitory effect of androgens on the growth of human breast carcinoma cells ZR-75-1 has also been observed in vivo.

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SUMM . . . the specific inhibitory effects of androgen therapy could be additive to the standard treatment limited to blockade of estrogens by **antiestrogens**.
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SUMM . . . breast cancer, would have undesirable deleterious effects on bone mass in women. Similarly, blockade of estrogens, a common treatment for **endometriosis**, has similar undesirable deleterious effects on bone mass in women.
SUMM . . . object of the present invention to provide a method for prevention and treatment of breast cancer, endometrial cancer, osteoporosis and **endometriosis**, while substantially avoiding undesirable side effects.
SUMM . . . of said androgenic steroid described herein are particularly useful for the treatment of human breast or endometrial cancer, osteoporosis or **endometriosis**. It is believed that the methods are also suitable for all purposes which are enhanced by administering androgens or otherwise. . .
DETD . . . breast and endometrial cancer as well as other diseases responsive to activation of the androgen receptor, e.g. bone loss and **endometriosis**. In this invention, the amount of the androgenic compounds administered is much lower than previously used in art for the. . .
DETD . . . scan, chest X-Ray, skeletal survey, ultrasonography of the liver and liver scan (if needed), CAT scan, MRI and physical examination. **Endometriosis** can be diagnosed following pains or symptoms associated with menstruations in women while definitive diagnosis can be obtained by laparascopy. . .
DETD . . . prevent other signs and symptoms of menopause. In women, when estrogen formation and/or action has been blocked for treatment of **endometriosis**, leiomyomata, breast cancer, uterine cancer, ovarian cancer or other estrogen-sensitive disease, administration of the androgen can be started at any. . .
DETD . . . for use in the prevention and treatment of breast and endometrial cancer as well as bone loss and treatment of **endometriosis** as discussed above. The kits or packages may also contain instructions on how to use the pharmaceutical compositions in accordance. . .
DETD . . . the above therapy using the described regimen, tumor growth of breast and endometrial cancer as well as bone loss and **endometriosis** can be relieved while minimizing adverse side effects. The use of the described regimen can also prevent appearance of the. . .

L11 ANSWER 10 OF 10 USPATFULL
AB Novel compounds for the inhibition of sex steroid activity for the treatment of both androgen-related and estrogen-related diseases include for example 15- and 16-halo substituted compounds such as: ##STR1## The compounds are characterized by an estrogenic nucleus substituted with a substituent of the formula --R.sup.1 [B--R.sup.2 --].sub.x L--G wherein

at least one of L and G is a polar moiety distanced from a ring carbon of the estrogenic nucleus by a least three intervening atoms:

x is an integer from 0-6;

R.sup.1 and R.sup.2 are independently either absent or selected from the group consisting of straight- or branched-chain alkylene, straight- or branched-chain alkynylene, straight- or branched-chain alkenylene, phenylene, and fluoro-substituted analogs of the foregoing; and

B is either absent or selected from the group consisting of --O--, --Se--, --SO--, --SO.sub.2 --, --NR.sup.3 --, --SiR.sup.3.sub.2, --CR.sup.3 OR.sup.3 --, NR.sup.3 CO--, NR.sup.3 CS--, --CONR.sup.3 --, CSNR.sup.3 --, --COO--, --COS--, --SCO--, --CSS--, --SCS--, --OCO-- and phenylene (R.sup.3 being hydrogen or lower alkyl).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	93:31404 USPATFULL	
TITLE:	Estrogen nucleus derivatives for use in inhibition of sex steroid activity	
INVENTOR(S):	Labrie, Fernand, Ste-Foy, Canada Merand, Yves, Ste-Foy, Canada	
PATENT ASSIGNEE(S):	Endorecherche Inc., Canada (non-U.S. corporation)	
	NUMBER	DATE
PATENT INFORMATION:	US 5204337	19930420 <--
APPLICATION INFO.:	US 1992-917915	19920721 (7)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1989-377010, filed on 7 Jul 1989, now abandoned which is a continuation-in-part of Ser. No. US 1989-322154, filed on 10 Mar 1989 which is a continuation-in-part of Ser. No. US 1988-265716, filed on 1 Nov 1988, now abandoned which is a continuation-in-part of Ser. No. US 1988-265150, filed on 31 Oct 1988, now abandoned	
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ASSISTANT EXAMINER:	Datlow, Philip I.	
LEGAL REPRESENTATIVE:	Ostrolenk, Faber, Gerb & Soffen	
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EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)	
LINE COUNT:	1657	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5204337 19930420 <--

SUMM This invention relates to novel inhibitors of sex steroid activity such as **antiestrogen** compounds having effective antagonistic capability while substantially lacking agonistic effects. More particularly, certain preferred embodiments of the invention relate to. . .

SUMM . . . the amount of sex steroid available to act at these sites. For example, alternative or concurrent therapy to administration of **antiestrogens** could involve attempts to block the production of estrogens (e.g. by ovariectomy) such that less is available to activate receptor. . .

SUMM There is, therefore, a need in the art for **antiestrogens** which effectively block estrogen receptors with minimal or no agonistic effect. Numerous compounds have been tried in the art with mixed results. Known **antiestrogens** continue to exhibit undesirable agonistic activity. See, for instance, Wakeling and Bowler, "Steroidal Pure **Antioestrogens**", J. Endocrinol. (1987) 112, R7-R10. The net effectiveness of prior art compounds is determined by the balance between their agonistic. . .

SUMM In U.S. Pat. No. 4,094,994, it is disclosed that the use of certain

antiestrogens may inhibit certain human breast tumor cells.

SUMM H. Mooridsen et al., Cancer Treatment Review 5, 131-141, (1978), discloses that Tamoxiphen, an **antiestrogen**, is effective in remission of advanced breast cancer in about 30 percent of the women patients treated.

SUMM The combined used of the **antiestrogen** Tamoxiphen and a luteinizing hormone-releasing hormone agonist, Buserelin, is also known for treatment of breast cancer. See, for instance, Klijn. . .

SUMM . . . male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g., by use of an **LHRH agonist**, e.g., [D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]LHRH ethylamide. The treatment includes administering an antiandrogen, e.g., flutamide in association with at least one inhibitor. . .

SUMM U.S. Pat. No. 4,472,382 relates to a method of treating prostate cancer using the combination of an antiandrogen and an **LHRH agonist**.

SUMM It is another object of the invention to provide a steroidal pure **antiestrogen** for therapeutic use.

SUMM It is another object to provide an **antiestrogen** having good affinity for estrogen receptors, but substantially lacking undesirable agonistic activity regarding these receptors and substantially lacking hormonal activity.

SUMM . . . in the treatment of estrogen-related diseases. These diseases include, but are not limited to, breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

SUMM . . . also be useful in male contraception. Estrogen-related diseases include but are not limited to breast cancer, uterine cancer, ovarian cancer, **endometriosis**, uterine fibroma, precocious puberty and benign prostatic hyperplasia.

SUMM . . . of inhibiting the activity of androgens and estrogens, respectively. For example, estrogen activity inhibitors include, but are not limited to **antiestrogens** which block estrogen receptors, thereby making them unavailable to estrogen compounds which could otherwise activate those receptors. Sex steroid activity. . .

DRWD FIG. 1 is a graph illustrating the antiestrogenic activity of one preferred **antiestrogen** of the invention.

DRWD FIG. 2 is a graph illustrating that the **antiestrogen** which is the subject of FIG. 1 is also a good inhibitor of sex steroid synthesis.

DETD Efficacy of an **antiestrogen** synthesized in accordance with Example 1

DETD . . . Scheme 2 above is an estrogen activity inhibitor. "EM 139" has been tested both for efficacy in acting as an **antiestrogen** by blocking estrogen receptors without substantially activating those receptors, (see FIG. 1 and explanation below) and for efficacy in inhibiting. . .

DETD . . . adult female ovariectomized Balb/c mice (body weight=19-20 g) sacrificed five days after ovariectomy. Ovariectomized mice injected with estradiol and no **antiestrogen** had a resultant uterine weight as shown by the shaded area designated "OVX +E.sub.2 " in FIG. 1.

The baseline uterine weight for a control group of ovariectomized mice injected with neither estradiol nor **antiestrogen** is represented in FIG. 1 by "OVX". The **antiestrogen** "EM 139", and estradiol dissolved in ethanol were injected subcutaneously in the appropriate test groups in a solution of 0.9%. . .